09/076,115

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PRIMERC.DWPI,EPAB,JPAB,USPT.	2
PRIMERD.DWPI,EPAB,JPAB,USPT.	2
PRIMERE.DWPI,EPAB,JPAB,USPT.	6
PRIMERF.DWPI,EPAB,JPAB,USPT.	1
PRIMERM.DWPI,EPAB,JPAB,USPT.	1
PRIMERN.DWPI,EPAB,JPAB,USPT.	1
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Search History

Today's Date: 9/28/2001

DB Name	Query	Hit Count	Set Name
USPT,JPAB,EPAB,DWPI	l2 and (primer$1 near5 cleavage)	6	L3
USPT,JPAB,EPAB,DWPI	l1 and reverse transcriptase	89	L2
USPT,JPAB,EPAB,DWPI	primer$1 near5 (ligand$1 or label$2) near5 exten$	188	L1

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Search Results - Record(s) 1 through 6 of 6 returned.

☐ 1. Document ID: US 6077664 A

L3: Entry 1 of 6 File: USPT Jun 20, 2000

US-PAT-NO: 6077664
DOCUMENT-IDENTIFIER: US 6077664 A

TITLE: Thermophilic DNA polymerases from Thermotoga neapolitana

DATE-ISSUED: June 20, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Slater; Michael R.	Madison	WI	N/A	N/A
Huang; Fen	Madison	WI	N/A	N/A
Hartnett; James R.	Fitchburg	WI	N/A	N/A
Bolchakova; Elena	Foster City	CA	N/A	N/A
Storts; Douglas R.	Madison	WI	N/A	N/A
Otto; Paul	Madison	WI	N/A	N/A
Miller; Katharine M.	Verona	WI	N/A	N/A
Novikov; Alexander	Foster City	CA	N/A	N/A
Velikodvorskaya; Galina A.	Moscow	N/A	N/A	RUX

US-CL-CURRENT: 435/6; 435/183, 435/320.1, 435/91.1, 435/91.2, 530/350, 536/23.2, 536/23.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5756702 A

L3: Entry 2 of 6 File: USPT May 26, 1998

US-PAT-NO: 5756702
DOCUMENT-IDENTIFIER: US 5756702 A

TITLE: Detection of nucleic acids in cells by thermophilic strand displacement amplification

DATE-ISSUED: May 26, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lohman; Kenton L.	San Jose	CA	N/A	N/A
Ostrerova; Natalie V.	Mountain View	CA	N/A	N/A
Van Cleve; Mark	Durham	NC	N/A	N/A
Reid; Robert Alan	Durham	NC	N/A	N/A

US-CL-CURRENT: 536/24.33; 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 5733752 A

L3: Entry 3 of 6 File: USPT Mar 31, 1998

US-PAT-NO: 5733752
DOCUMENT-IDENTIFIER: US 5733752 A

TITLE: Detection of nucleic acids in cells by thermophilic strand displacement amplification

DATE-ISSUED: March 31, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lohman; Kenton L.	San Jose	CA	N/A	N/A
Ostrerova; Natalie V.	Mountain View	CA	N/A	N/A
Cleve; Mark Van	Durham	NC	N/A	N/A
Reid; Robert Alan	Durham	NC	N/A	N/A

US-CL-CURRENT: 435/91.2; 435/5, 435/6, 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 5712124 A

L3: Entry 4 of 6 File: USPT Jan 27, 1998

US-PAT-NO: 5712124
DOCUMENT-IDENTIFIER: US 5712124 A

TITLE: Strand displacement amplification

DATE-ISSUED: January 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Walker; George Terrance	Chapel Hill	NC	N/A	N/A

US-CL-CURRENT: 435/91.2; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 5631147 A

L3: Entry 5 of 6 File: USPT May 20, 1997

US-PAT-NO: 5631147
DOCUMENT-IDENTIFIER: US 5631147 A

TITLE: Detection of nucleic acids in cells by thermophilic strand displacement amplification

DATE-ISSUED: May 20, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lohman; Kenton L.	San Jose	CA	N/A	N/A
Ostrerova; Natalie V.	Mountain View	CA	N/A	N/A
Cleve; Mark V.	Durham	NC	N/A	N/A
Reid; Robert A.	Durham	NC	N/A	N/A

US-CL-CURRENT: 435/91.2; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5550025 A

L3: Entry 6 of 6 File: USPT Aug 27, 1996

US-PAT-NO: 5550025
DOCUMENT-IDENTIFIER: US 5550025 A

TITLE: Detection of hydrophobic amplification products by extraction into an organic phase

DATE-ISSUED: August 27, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Walker; G. Terrance	Chapel Hill	NC	N/A	N/A

US-CL-CURRENT: 435/6; 435/91.2, 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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L3: Entry 5 of 6 File: USPT May 20, 1997

DOCUMENT-IDENTIFIER: US 5631147 A
TITLE: Detection of nucleic acids in cells by thermophilic strand displacement amplification

DEPR:
It is an important feature of the present invention that either RNA or DNA target sequences, or both, may be amplified directly using the inventive methods. To amplify only RNA, a reverse transcriptase may be added to the tSDA reaction as it is in reverse transcription PCR (rtPCR--G. J. Nuovo, et al. 1992. Diag. Molec. Pathol. 1, 98-102; G. J. Nuovo, et al. 1991. Am. J. Pathol. 58, 518-523; G. J. Nuovo, et al. 1991. Am. J. Pathol. 139, 1239-1244). However, several of the DNA polymerases used in tSDA have now been found to exhibit reverse transcriptase activity. They can polymerize DNA copies of a target sequence using either RNA or DNA as the template, with incorporation of dNTP.alpha.S and displacement from a nick. RNA target sequences may therefore be reverse transcribed by the same polymerase which performs the DNA amplification portion of the tSDA reaction, without the need to add a separate reverse transcriptase. RNA may be amplified in the cells (i.e., without substantial amplification of DNA targets) by eliminating the heat denaturation step or treating with DNase prior to initiating the tSDA reaction. The double stranded DNA in the cells then remains double stranded and unavailable as a template, whereas primers can hybridize to available single stranded RNA and begin specific amplification of RNA target sequences by generating cDNA. The cDNA in turn serves as a template for further amplification. Specific amplification of RNA target sequences may also be accomplished by treating the cells with RNase-free DNase prior to initiating SDA. As fixation aids in maintaining the integrity of the cells during heating, fixing may not be needed when there is no preliminary heat denaturation step. It may still be useful, however, to permeabilize the unfixed cells or tissues

DEPR:
If the heat denaturation step is included (without RNase treatment) prior to annealing of the SDA primers, both DNA and RNA target sequences will be amplified. In situ reverse transcription of RNA by the DNA polymerases used in tSDA is generally less efficient than DNA synthesis, but has unexpectedly been found in some cases to be more efficient than conventional reverse transcriptases. However, RNA targets are usually present in the cell in greater numbers than the corresponding DNA target, and the high efficiency of amplification of the cDNAs which are generated quickly overcomes and compensates for any reduced efficiency in the reverse transcription step of the reaction. Amplification of both RNA and DNA targets is preferred for most diagnostic applications of the invention because this gives the greatest number of amplifiable target sequences per cell and, as a result, the greatest sensitivity and largest number of potentially positive cells per sample.

DEPR:
Restriction endonucleases suitable for SDA must cleave only one of the strands of a double stranded hemimodified recognition/cleavage site for the restriction endonuclease ("nicking"). This nicking activity is of great importance, as it is nicking which perpetuates the reaction and allows subsequent rounds of target amplification to initiate. Because restriction enzymes generally produce double strand breaks, cleavage of one of the two strands in the duplex cleavage site must be selectively inhibited. This is usually accomplished by introducing nucleotide analogs (e.g., deoxynucleoside phosphorothioates) into one strand of the DNA during synthesis so that either the modified strand or the unmodified strand is no longer susceptible to cleavage. In cases where the unmodified strand is protected from cleavage, nucleotide analogs may be incorporated into the

primer during its synthesis, thus eliminating both the need to add nucleotide analogs to the amplification reaction and the requirement that the polymerase be capable of incorporating such nucleotide analogs.

DEPR:
Alternatively, amplification products may be detected in situ or after release from the cells by primer extension as described by Walker, et al. (1992b), supra. In the primer extension method an oligonucleotide primer comprising a detectable label is hybridized to the amplification products and extended by addition of polymerase. For detection the primer may be 5' end-labeled, preferably using .sup.32 P or a fluorescent label. Alternatively, extension of the hybridized primer may incorporate a dNTP analog comprising a directly or indirectly detectable label. For example, extension of the primer may incorporate a dig-derivatized dNTP, which is then detected after extension by reaction with AP-.alpha.-dig and a suitable AP substrate. The primer to be extended may either be the same as an amplification primer or it may be a different primer which hybridizes to a nucleotide sequence in the amplicon which is between the binding sites of the amplification primers.

DEPR:
The label of the hybridized detector probe, extended primer, amplicon or secondary amplification product is then detected, preferably in situ, as an indication of the presence of amplified target sequences. This may require the addition of reagents to the cells to develop the signal of an indirectly detectable label such as AP, biotin or dig. Microscopic analysis of the cells is preferred when the detectable label is an enzyme. Microscopic analysis may be either by visual observation of the cells or tissues (fluorescence or light microscopy), or automated image analysis using instruments such as DISCOVERY (Becton Dickinson Image Cytometry, Leiden, Holland) to evaluate the number and signal intensity of positive cells. When the label is a radiolabel, the cells may be suspended in scintillation fluid and the signal detected by scintillation counting. Use of a directly detectable fluorescent label allows fluorescence analysis of cells in suspension by flow cytometry (e.g., FACSCAN, Becton Dickinson Immunocytometry Systems, San Jose, Calif.). A shift in peak fluorescence to the right on a plot of cell number vs. fluorescence intensity is indicative of an increased number of cells containing the target sequence. Conversely, a shift in peak fluorescence to the left on the plot is indicative of a reduced number of cells containing the target sequence. Alternatively, amplification products may be released from cells prior to detection as described above or visualized after gel electrophoresis as bands of amplification products, e.g., by EtBr staining, hybridization of a detector probe or primer extension. When a radiolabel is used for the primer or detector probe, amplification products may be visualized by autoradiography of the gels.

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L3: Entry 6 of 6 File: USPT Aug 27, 1996

DOCUMENT-IDENTIFIER: US 5550025 A
TITLE: Detection of hydrophobic amplification products by extraction into an organic phase

BSPR:
P. M. Holland, et al. (1992. Clin. Chem. 38, 462-463) describe a method for detecting amplification products of PCR in which the 5'-3' exonuclease activity of Taq DNA polymerase is used to generate target amplification-specific signal by digestion of a labeled probe hybridized downstream of the amplification primer. The labeled probe is not extendable, possibly because certain of the detection systems described make use of a 3' end-label. Further, an extendable labeled probe would function as a PCR amplification primer, thereby increasing non-specific background signal in the reaction. Cleaved probe fragments are generated during amplification, and may be differentiated from uncleaved probe in a variety of ways, depending on the type of probe label. The authors suggest thin-layer chromatography or capture by a 3' biotin label to separate cleaved from uncleaved probe, or sequencing. These detection methods require cumbersome and time consuming manipulations of the sample after amplification. The present methods for primer-based detection of target amplification also make use of a single amplification reaction to concurrently generate secondary products for detection. In contrast to P. M. Holland, et al. and other prior art methods, however, the secondary amplification products are detected in a simple format by extraction into an organic phase.

BSPR:
An amplification primer is a primer for amplification of a target sequence by primer extension. For SDA, the 3' end of the amplification primer (the target binding sequence) hybridizes at the 3' end of the target sequence. The amplification primer comprises a recognition site for a restriction endonuclease near its 5' end. The recognition site is for a restriction endonuclease which will cleave one strand of a DNA duplex when the recognition site is hemimodified ("nicking"), as described by Walker, et al. (1992. PNAS, supra). A hemimodified recognition site is a double stranded recognition site for a restriction endonuclease in which one strand contains at least one derivatized nucleotide which causes the restriction endonuclease to nick the primer strand rather than cleave both strands of the recognition site. Usually, the primer strand of the hemimodified recognition site does not contain derivatized nucleotides and is nicked by the restriction endonuclease. Alternatively, the primer may contain derivatized nucleotides which cause the unmodified target strand to be protected from cleavage while the modified primer strand is nicked. Such restriction endonucleases can be identified in routine screening systems in which a derivatized dNTP is incorporated into a restriction endonuclease recognition site for the enzyme. The preferred hemimodified recognition sites are hemiphosphorothioated recognition sites for the restriction endonucleases HincII, HindII, AvaI, NciI, Fnu4HI, BsoBI and BsrI. The amplification primer also comprises a 3'--OH group which is extendable by DNA polymerase when the target binding sequence of the amplification primer is hybridized to the target sequence. For the majority of the SDA reaction, the amplification primer is responsible for exponential amplification of the target sequence. As no special sequences or structures are required, amplification primers for PCR generally consist only of target binding sequences.

DEPR:
In a preferred PCR method according to the invention, lipophilic secondary amplification products may be generated from a hydrophilic signal primer in a

target amplification-dependent manner by employing a lipophilic label in the PCR methods of P. M. Holland, et al., supra. Referring to the Figure at page 462 of the publication, Taq DNA polymerase extends the amplification primer and displaces the first few nucleotides of the hybridized downstream probe (i.e., the signal primer), cleaving the signal primer at the phosphodiester bond joining the displaced region with the remaining base-paired portion of the signal primer. This releases a labeled secondary amplification cleavage product with significantly fewer nucleotides linked to the lipophilic label (usually 1-2). This cleavage product is generated in a target amplification-dependent manner (i.e., only upon hybridization and extension of amplification primers and signal primers on a target sequence), as the partially double-stranded "fork" structure is the preferred substrate for cleavage. The lipophilic label with the reduced number of linked nucleotides can then be transferred to an organic phase for detection as an indicator of target amplification. As generation of lipophilic cleavage products in this system does not require that the 5' end of the signal primer be double-stranded, the 3'-end of the signal primer may be unextendable as described by the authors. Alternatively, the 3' end of the signal primer may be extendable without interfering with generation, phase transfer and detection of the lipophilic cleavage product. However, an extendable signal primer may increase background and extending the signal primer unnecessarily reduces the efficiency of the polymerase in amplification. The number of nucleotides linked to a selected lipophilic label can be varied by varying the nucleotide sequence of the signal primer. Higher A+T content in the 5' end of the signal primer facilitates generation of larger, less lipophilic cleavage products as a result of more efficient displacement by Taq polymerase and/or "breathing" of the duplex before cleavage. Conversely, increased G+C content generally reduces the size of the cleavage product and increases its lipophilicity. Such routine variation of the sequence of the signal primer may therefore be used to optimize the length of the cleavage product for a selected label and a selected organic phase. Alternatively, the number of nucleotides linked to the lipophilic label in the cleavage product may be increased by inclusion of a non-hybridizing tail in the signal primer between the lipophilic label and the target binding sequence of the signal primer. However, as previously stated, more lipophilic secondary amplification products having fewer linked nucleotides are generally preferred.

DEPR:
For adaptation of the inventive methods to 3SR, it is only necessary to employ a 5'.fwdarw.3' exonuclease deficient reverse transcriptase with strand displacing activity in the 3SR reaction, with hybridization of a signal primer to the RNA target downstream of the "3' primer" and/or the "5' primer" of Guatelli, et al., supra (see Guatelli's FIG. 1, page 1875). In a reaction scheme similar to Applicant's FIG. 1, the hybridized signal primer containing the restriction endonuclease recognition sequence is 1) extended, and 2) displaced by extension of the upstream DNA primer. The displaced extension product is then made double stranded by hybridization and extension of the other primer. This renders the restriction endonuclease recognition site cleavable, and a lipophilic secondary amplification product is generated for transfer to the organic phase. Also similar to SDA, the signal primer for 3SR does not contain a T7 RNA polymerase promoter sequence and therefore cannot function as an amplification primer, reducing nonspecific background signal.

DEPR:
The IS6110 target sequence is amplified by PCR in the presence of the amplification primers and the signal primer, essentially as described by R. K. Saiki, et al. (1985. Science 230, 1350-1354) and K. B. Mullis, et al. (1987. Methods Enzymol. 155, 335-350) utilizing the 5'.fwdarw.3' exonuclease activity of Taq DNA polymerase to generate target-amplification specific signal primer cleavage products as described by Holland, et al., supra. After stopping the amplification reaction, an organic solvent is added to the aqueous reaction phase and mixed. The phases are separated (e.g., by centrifugation) and the organic phase is assayed for presence of the dye using methods appropriate for detection of the selected dye. If an increase in the amount of dye transferred to the organic phase as compared to an unamplified control reaction is detected, the target sequence is present and has been amplified. If no increase is detected, the target sequence is not present or is present but has not been amplified.